REMARKS

I. Introduction

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 2, 4, 6, and 8-10 are requested to be cancelled. The cancellation of claims does not constitute acquiescence in the propriety of any rejection set forth by the Examiner. Applicants reserve the right to pursue the subject matter of the canceled claims in subsequent divisional applications.

Claims 1 and 22 are currently being amended. Exemplary support for the amendment is found in the specification and in originally filed claim 2.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claims remain under examination in the application, is presented, with an appropriate defined status identifier.

Upon entry of this Amendment, claims 1, 3, 5, 7, 11-18 and 20-40 will remain pending in the application, with claims 33-40 withdrawn from consideration in response to a restriction requirement and claims 1, 3, 5, 7, 11-18 and 20-32 ready to be examined on the merits.

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

II. Response to Issues Raised by Examiner in Outstanding Office Action

Claims 1-18 and 20-32 are rejected by the Examiner under 35 U.S.C. § 103 as being obvious over Eppstein (WO 92/29134) in view of Bellhouse et al. (USP 5,630,796). Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner asserts that Eppstein teaches a method of enhancing the permeability of a permeant across a biological membrane, including skin and mucosa using microporation of the membrane at the site of administration, followed by contacting the porated surface by the active agent and a permeation enhancer. The Examiner asserts that Eppstein suggests forming the pores using any non-invasive means that do not require entry of a needle to the skin or mucosa or use of any invasive instruments. The Examiner notes, that Eppstein does not teach use of a needeless syringe to form the skin pores. However, the Examiner asserts that it would have been obvious to a person of ordinary skill in the art to use the needeless syringe disclosed by Bellhouse in the method of Eppstein in order to arrive at the claimed invention. Applicants respectfully disagree with the Examiner.

To establish a *prima facie* case of obviousness, there needs to be (1) some suggestion or motivation to modify the reference or to combine reference teachings, (2) a reasonable expectation of success, and (3) the prior art references, when combined, must teach or suggest all the limitations of the claimed invention. *See* MPEP §2143 (Aug. 2001). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Applicants respectfully assert that the examiner has not met his burden.

a. The combined teachings of Eppstein and Bellhouse do not Teach or Suggest Each and Every Limitation of the Claimed Invention

Applicants have amended claim 1 to recite that the particles comprise the therapeutic agent.

The Examiner has failed to establish a *prima facie* case of obviousness because the combined teachings of Eppstein and Bellhouse do not teach or suggest each and every limitation of the claimed invention. Eppstein relates to a method where a surface is prepared by microporation for subsequent administration of a therapeutic agent. The method of Eppstein involves a two step process. Firstly, a biological membrane is prepared for the administration of a therapeutic agent by microporation, and secondly, the biological membrane which has been prepared in this way is contacted with a therapeutic agent and permeation enhancer. In contrast, amended claim 1 is directed to a method for enhancing the

flux or improving the uptake of a therapeutic agent which is administered at the same time that microporation takes place. In the claimed method, microporation is carried out at the same time as administration of the therapeutic agent. After the therapeutic agent has been administered, a transdermal delivery device or an occlusive dressing is positioned over the area of skin or mucosa which has been microporated and to which the therapeutic agent has (already) been administered.

The Examples in the specification illustrate the method of claim 1. Examples 1 and 2 demonstrate how the flux of insulin administered using a needleless syringe may be enhanced using an occlusive dressing, Example 3 demonstrates how the immunogenicity of a particulate HBV vaccine composition administered using a needleless syringe may be enhanced using an occlusive dressing, and Example 4 demonstrates how the uptake of calcitonin administered using a needleless syringe may be enhanced using an occlusive dressing. In each of these examples, the therapeutic agent is administered at the same time as microporation takes place and the application of an occlusive dressing takes place subsequent to administration of the therapeutic agent/microporation.

b. Eppstein Teaches Away from the Method of Claim 1

Eppstein arguably teaches away from the claimed invention because Eppstein teaches that microporation and the administration of a therapeutic agent are two separate steps that must be carried out sequentially.

Furthermore, the active agents that may be used in the method described by Eppstein include polypeptides and vaccines, optionally associated with a carrier. At page 14, line 25, to page 15, line 1, in particular, Eppstein refers to the use of carriers which comprise liposomes, lipid complexes, microparticles or polyethylene glycol compounds. Although Eppstein refers to microparticles, these microparticles are not particles that are intended for use with a needleless syringe. Instead, it appears that the microparticles disclosed by Eppstein have a lipid or polymer content. Such microparticles would likely not have the necessary strength to withstand the forces associated with delivery from a needleless syringe. That is to say, it does not seem that such microparticles would have sufficient structural integrity to withstand being fired from a needleless syringe and impacting skin or mucosal tissue at the very high

velocities that are necessarily associated with administration from a needleless syringe. This may be contrasted with the particles used in Example 1 of the present application. Example 1 describes the use of a particulate insulin formulation prepared using specific steps (lyophilisation, compression and milling) so as to ensure that the density of the particles is high enough for transdermal/transmucosal delivery at supersonic velocities. There is no suggestion in Eppstein that such steps should be taken. Therefore, it does not appear to be possible to use the particles in Eptstein with a needleless syringe. By teaching particles that are not intended for use with a needleless syringe, Eppstein teaches away from the claimed invention.

c. A Person of Ordinary Skill in the Art Would Not Have Been Motivated to Combine the Teachings of Eppstein and Bellhouse

The Examiner states that a person of ordinary skill in the art would have been motivated to combine the teachings of Eppstein and Bellhouse to arrive at the claimed invention because Bellhouse teaches that the needleless method is "a safe and quick method with less pain and no risk of infection." Applicants respectfully disagree.

As discussed above, the Examiner has failed to establish a prima facie case of obvious because the combination of Eppstein and Bellhouse does not teach each and every limitation of the claimed invention. However, assuming *arguendo* that the combined teachings did teach each and every limitation of the claimed invention, a person of ordinary skill in the art would not have been motivated to combine the teachings of Eppstein and Bellhouse because Bellhouse teaches that the disclosed method should not be combined with other methods. For example, Applicants direct the Examiner's attention to the passage at column 1, lines 45 to 48 which explains that the needleless syringe is "useful for routine delivery of drugs, such as insulin..., and could be of use in mass immunisation programs, or for the delivery of slow release drugs such as pain killers and contraceptives". Thus, Bellhouse makes it clear that the needleless syringe it describes is useful merely for the routine delivery of drugs and cannot reasonably be expected to be of use in a multi-step drug delivery technique, such as the method of claim 1, in which different drug delivery technologies are used to custom tailor drug delivery profiles. Therefore, Bellhouse would not have motivated a skilled artisan to combine its teachings with the teachings of Eppstein.

Furthermore, Eppstein would have motivated a skilled artisan to combine its teachings with Bellhouse. The types of microporation envisaged by Eppstein are described at page 16, lines 14 to 24. There, Eppstein describes a number of techniques which may be used for porating a biological membrane. However, Eppstein does not mention the use of particles administered via a needleless syringe. The passage does mention the use of a high pressure jet of fluid, but that disclosure occurs in the context of using the fluid itself to hydraulically puncture the biological membrane; this is of course different from using a fluid to propel a particle across the biological membrane as would be the case with a needleless syringe. It is

clear therefore that Eppstein does not disclose the use of a needleless syringe and does not provide the necessary motivation for a person of ordinary skill in the art to combine its teachings with Bellhouse.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

It is acknowledged that the foregoing amendments are submitted after final rejection. However, because the amendments do not introduce new matter or raise new issues, and because the amendments either place the application in condition for allowance or at least in better condition for appeal, entry thereof by the Examiner is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant(s) hereby petition(s) for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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